EXHIBIT A

AUTHOR: W. Wayt Gibbs
TITLE: Shrinking to Enormity
SOURCE: Scientific American v284 no2 p33-4 F 2001

A small start-up firm in Santa Clara, Calif., had a big idea five years ago. By adapting the methods of microprocessor manufacturing, it created microchips that contain thousands of distinct DNA probes on glass in place of transistors on silicon. The company figured that researchers would immediately find such "gene chips" useful, and doctors would eventually find them indispensable. With a chip, a tissue sample and a scanner, a technician can get a snapshot of the secret lives of the cells in that tissue, a detailed picture showing which genes are most active and which have been silenced. The idea that this might lead to customized preventive medical treatments was a compelling one for investors, who bid the stock of Affymetrix up 2,700 percent from July 1996 to March 2000.

Success like that attracts competition, and numerous companies now make several different kinds of DNA microarrays. All the chips work on the same principle: the glass is coated with a grid of tiny spots, 20 to 100 microns diameter; each spot contains millions of copies of a short sequence of DNA; and a computer keeps track of which DNA sequences are where. To make their snapshot, scientists extract from their sample cells messenger RNA (mRNA). Using enzymes, they make millions of copies of the mRNA molecules, tag them with fluorescent dye and break them up into short fragments. The tagged fragments are washed over the chip and, overnight, perform a remarkable feat of pattern matching, randomly bumping into the DNA probes fixed to the chip until they stick to one that contains a perfect genetic match. Although there are occasional mismatches, the millions of probes in each spot ensure that it lights up only if complementary mRNA is present. The brighter the spot fluoresces when scanned by a laser, the more mRNA of that kind was in the cell.

Affymetrix now makes more than 100,000 chips a year using light, masks and photosensitive chemicals to build DNA probes on chips one nucleotide at a time. Agilent, Hitachi and Protogene Laboratories, among others, use modified ink-jet printers, whose heads squirt A, T, G and C nucleotides instead of cyan, magenta, yellow and black inks. Canon is reportedly working with bubble jets to deposit DNA sequences, whereas Corning, Motorola and Incyte Genomics employ precision robots that place microdroplets of presynthesized sequences onto prepared slides. Although firms are spreading into almost every viable niche, none has yet submitted a medical diagnostic to the U.S. Food and Drug Administration for approval. Beyond the relatively straightforward obstacles—gene chip systems are still too expensive, for example, and few doctors know how to interpret their results—lies a much deeper question.

"Humans populations are outbred," remarks Lee Hartwell, director of the Fred Hutchinson Cancer Research Center in Seattle. Even well-understood genetic diseases involve myriad possible mutations; more than 1,000 have been linked to cystic fibrosis, for instance. An accurate diagnostic chip may have to include them all.

Although it may be many years before DNA microarrays find routine use by physicians, they have already begun to change experimental biology in profound ways. "They allow us to be vastly more productive—by a factor of 1,000 or so," says Richard A. Young of the Whitehead Institute for Biomedical Research of the Massachusetts Institute of Technology. In December 2000 his group reported that they had used

microarrays for yeast to rediscover, in a matter of weeks, seven genes known to control a particular protein—research that originally took about 30 scientist-years to complete by conventional means. And the microarray experiments identified three additional genes that had been missed.

"The productivity boost is great," Young continues. "But what microarrays are really useful for is asking radically new questions about an entire system. At the moment, we understand how only half a dozen genes in any organism are regulated. If we knew the complete regulatory circuitry—how all genes are turned on or off and coordinate their activity with one another to deal with the environment—such a map would vastly increase our capacity to develop drugs for serious medical problems."

A team led by Timothy R. Hughes and Matthew J. Marton of Rosetta Inpharmatics in Kirkland, Wash., recently demonstrated one way to sketch such a map. Using some 700 chips, the scientists measured what happened to every gene in yeast cells when they were perturbed in 300 different ways: they deleted 279 genes and treated the cells with 13 different drugs. The study was able to work out the function of eight mysterious yeast genes, pinpoint the target of a common drug and even uncover a strong clue to a new human gene involved in cholesterol production. The project mined 10 million data points, in which more nuggets of knowledge undoubtedly remain.

With each successive generation of microarray technology, the size of the probe spots shrinks, the number of genes per chip rises, and biologists' schemes for using the devices swell in grandeur. "We can now put over 60 million probes on a single glass wafer," Fodor says excitedly. He figures the entire human genome will fit on 200 to 300 wafers. And in fact, in September, Affymetrix spun off Perlegen, a subsidiary that plans to use microarrays to sequence, from scratch, the genomes contained in both chromosomes of 50 people to detect the subtle variations both within and among them. "In these patterns we will find the signature of human evolution. The potential for scientific discovery," Fodor boasts, "is fantastic."

So is the potential for confusion and error, Young and others caution. Hughes and Marton showed that genetic profiles are most powerful when compared with hundreds or thousands of others in a reference database. Such databases will be huge, because each profile contains about 50 megabytes of data. "How do we translate the data from an Affymetrix array to compare it with data from an array built by Corning?" Young asks. "It hasn't been done yet. And how do we encode the effects of one gene on another? It's all probabilistic, even though biologists tend to talk in terms of A causing B. We need a new mathematical language," he says. That may lead in turn, he suggests, to new theories that explain how the rich patterns of life arise from the complex chemistry of DNA.

ADDED MATERIAL

COURTESY OF AFFYMETRIX, INC.

DNA CHIPS in handheld housings can sense the on/off state of up to 400,000 genes in a tissue sample.

INNER LIFE OF CELLS is revealed by fluorescent spots on a microarray. The brightness of each spot increases as more messenger RNA from the cell perfectly matches (row A in inset) the unique DNA fragments stuck there. Slightly mismatched (row B) DNA sequences serve as controls. COURTESY OF AFFYMETRIX, INC.